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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,992	07/12/2001	Avi Ashkenazi	10466/76	8661

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/904,992	ASHKENAZI, ET AL	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 02 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *please see the attachment*.

3. ☒ Applicant's reply has overcome the following rejection(s): rejection of claim 44 for lack of written description.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *please see the attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *39-46 and 49-51*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit: 1636

ADVISORY ACTION ATTACHMENT

2. Non-Entry of the Amendment

The amended claims require additional amendment in order to correct grammatical errors that make it unclear as to what is claimed (e.g. "the amino acid sequence of the polypeptide (SEQ ID NO: 2)"-does this specify the entire sequence represented by SEQ ID NO: 2 or only a portion of the sequence?).

5. Request for Reconsideration

Arguments directed to the amended claims are moot, as the amendment has not been entered. Many of applicants' arguments are a repeat of arguments previously presented. In response, the examiner's comments and grounds of rejection are incorporated here by reference.

Response to Arguments/Utility

With regard to the rejection made under 35 U.S.C. 101 for lack of a substantial and specific utility, the response essentially argues: **1)** Exhibits A and B demonstrate how effective PRO302 is at inducing vascular permeability and show that it is easy to monitor the ability of polypeptides like PRO302 to induce vascular leakage compared to a negative and positive control, **2)** based on these results, the skilled artisan would know how to use anti-PRO302 antagonists (e.g. antibodies) to stop vascular leakage associated with different conditions (e.g. pulmonary leakage, capillary leakage, tumor leakage or in burns), **3)** such uses are substantial and specific and would be clearly evident to the skilled artisan, **4)** the MPEP 2107.01 states that the examiner should not interpret the phrase "immediate benefit to the public" or similar

formulations to mean that an invention must be currently available to the public in order to satisfy the utility requirement, and that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient to describe a "substantial" utility, and **5)** if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, the utility rejection should not be made.

At no point has the examiner cast the rejection in terms of a lack of credible utility. Rather, the rejection has been made in terms of a lack of a specific and substantial utility that does not require further experimentation to identify a real world use for the claimed invention. This does not, as the response implies, mean the examiner is applying a standard that the invention must be "readily available" to the public. There is no requirement that the invention be "readily available" to the public (e.g. already reduced to practice). Again, the grounds of rejection are directed to a lack of a specific, substantial utility that does not require further experimentation for confirmation of such utility.

For example, even though applicants' exhibits and specification clearly demonstrate that injection of the PRO302 protein intra-dermally in guinea pigs will cause some vascular leakage, there is no convincing evidence or rational that PRO302 plays any role whatsoever in vascular leakage in its usual role(s) *in vivo* (e.g. mediating vascular permeability in response to any particular condition or event such as burns or tumor growth). In other words, there is no convincing evidence or argument for a specific role for PRO302 in any process or condition that involves vascular integrity (e.g. pulmonary leakage, capillary leakage, tumor leakage or in burns). The fact is that applicants have only demonstrated that injection of large quantities of

this protein can cause some vascular leakage in lab rodents. The skilled artisan would still have had to confirm that PRO302 plays some role in vascular physiology as part of its normal functions in the body in order to demonstrate a substantial utility for the protein in identifying antagonists of this particular activity. One cannot consider that developing antagonists to a protein that may only be involved in disrupting vascular integrity upon injection in large quantities under the skin, a completely artificial situation, as a "real world" application in and of itself.

With regard to applicants' data presented in Exhibits A & B, it is clear that PRO302 does invoke at least some vascular leakage when injected intra-dermally in guinea pigs. It is noted, however, that the degree of induced permeabilization is substantially less for PRO302 as compared to the positive control, even when ten times as much (by weight) PRO302 protein is injected. It is conceded that the examiner has not done the calculations to determine the molar ration of PRO302/VEGF used in the experiments, nor taken into account any differences in activity that might be due to how the different proteins were prepared, but the data as presented in the Exhibits do not appear be so impressive as to suggest that PRO302 normally has a role in vascular permeabilization.

Response to Arguments/Enablement

With regard to the rejection made under 35 U.S.C. 112 1st paragraph for lack of enablement, the response filed 3/2/2004 essentially argues: **1)** the level of skill, knowledge and predictability in the art all must be considered in determining enablement, **2)** from the data disclosed in the specification (i.e. the vascular permeabilization assay), the skilled artisan would

know that PRO302 can be used as a target to develop therapeutic molecules that stop vascular leakage, **3)** it would not require undue experimentation to determine the use of such antagonists *in vivo*, **4)** the level of skill in the art at the time of filing was very sophisticated (e.g. M.D.'s and Ph.D.'s), and **5)** it would only have required routine skill in the art to evaluate how to stop vascular leakage *in vivo* with antagonists to PRO302.

The examiner made a reasoned analysis of all of the Wands factors in determining whether the rejected claims were enabled by the specification and state of the art at the time of filing. The assertion that the skilled artisan would have known, based on the data presented in the single working example, that PRO302 could be used to develop therapeutic molecules that stop vascular leakage is unsupported. As indicated above, there is no convincing evidence or rational provided by applicants' specification that PRO302 plays any role whatsoever in inducing vascular permeabilization under normal conditions (e.g. when not under the experimental conditions taught in the specification). Even if one assumes that PRO302 does play some normal role in inducing vascular permeability, which is in no way conceded here, there is no basis for one of skill in the art to assume that PRO302 mediates its effects in a manner analogous to VEGF. Therefor, one cannot simply use VEGF as a "roadmap" for determining how to make and use antagonists for PRO302. In the absence of significant guidance as to the actual role of PRO302 in the body, experimentation to identify and to determine the how to use PRO302 antagonists would necessarily have to be considered as undue, unpredictable experimentation.

Response to Arguments/Written Description

With regard to the rejection made under 35 U.S.C. 112 1st paragraph for lack of written description, the response filed 3/2/2004 essentially argues: **1)** claim 44 is drawn only to the full length PRO302 (or the mature protein lacking its signal sequence) and should not be rejected for lack of description, **2)** determination for a lack of description should be made in view of the level of knowledge and skill in the art and the teachings of the specification, **3)** the inventor is not required to describe every detail of their invention, **4)** the inventors' disclosure obligation varies according to the art to which the invention pertains, **5)** the level of skill in the field is relatively high (e.g. M.D.'s and Ph.D.'s), **6)** the specification provides sufficient detail concerning the cloning and expression of variants of the polypeptides like PRO302 (e.g. pages 112-117) and further disclosed that screening methods for secretory proteins were known in the art at the time of filing, **7)** the specification provides sufficient information about structural characteristics of the variants in the claimed genus and further demonstrates how variants could be obtained, and **8)** case law and the written description training materials clearly acknowledge that the written description requirements can be met by a combination of structural and functional characteristics shared by members of the genus, as is done in the instant case.

Applicants' arguments regarding claim 44 are persuasive and the rejection of claim 44 is withdrawn.

The examiner made a reasoned argument in view of the level of skill in the art and the level of guidance provided by the instant specification and prior art. The arguments concerning cloning/expressing genes and assays for screening secretory proteins are better suited to an enablement rejection rather than the instant grounds of rejection for lack of written description.

Such teachings do not provide a structural/functional basis for the skilled artisan to envision even *one* of the specific embodiments of applicants invention other than PRO302 that *necessarily* meet the functional limitations of the claims, much less a sufficient number of specific embodiments to describe the broadly claimed genus of such proteins. As stated in making the rejection, there is no significant guidance from the specification or prior art as to the functional domains of PRO302 required for the observed vascular permeabilization. Therefore, there was no basis at the time of filing for the skilled artisan to envision a sufficient number of variants of PRO302 that would necessarily permeabilize vascular tissue to describe the broadly claimed genus of such proteins. Thus, the skilled artisan would have reasonably concluded that applicants were not in possession of the claimed invention at the time of filing.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER